Abstract. Cholera-specific surveillance in Indonesia was initiated to identify the introduction of the newly recognized Vibrio cholerae non-O1, O139 serotype. Findings from seven years (1993–1999) of surveillance efforts also yielded regional profiles of the importance of cholera in both epidemic and sporadic diarrheal disease occurrence throughout the archipelago. A two-fold surveillance strategy was pursued involving 1) outbreak investigations, and 2) hospital-based case recognition. Rectal swabs were transported to Jakarta for culture and isolates were characterized by serotypic identification. Outbreak findings showed that V. cholerae O1, Ogawa serotype, was the predominant etiology in all 17 instances of investigated epidemic transmission. Monitoring of eight hospitals representing seven provinces provided 6,882 specimens, of which 9% were culture positive for V. cholerae: 589 (9%) for O1 and 20 (1%) for non-O1 strains. Proportional representation of V. cholerae O1 among cases of sporadic diarrheal illness was variable, ranging from 13% in Jakarta to <1% in Batam. Overall, 98% of V. cholerae O1 cases were the Ogawa serotype. There was no instance of non-O1, O139 serotype introduction in either epidemic or sporadic disease form. Anti-microbial drug susceptibility was consistently demonstrated, both temporally and spatially, except against colistin. Evidence is provided that epidemic and sporadic cholera occurrence in western Indonesia is associated with periods of low rainfall. Conversely, in the more eastern portion of the country, heavy rainfall may have contributed to epidemic cholera transmission.

INTRODUCTION

Epidemic and sporadic diarrheal transmission worldwide has been principally attributed to the O1 biotypes of Vibrio cholerae. The two O1 serotypes associated with cholera outbreaks and community acquired exposures are the classical biotype and El Tor biotype. The first six cholera pandemics of the last two centuries were believed to be largely substitutions of the classical biotype and El Tor biotypes. Attenuation, such as use of untreated water for bathing and some-
dertaken in Indonesia for the purpose of 1) identifying the emergence of *V. cholerae* O139 in the country; and 2) differentiating the relative importance of *V. cholerae* O1 biotypes and serotypes in both epidemic and sporadic, acute diarrheal disease occurrence.

**MATERIALS AND METHODS**

**Surveillance strategy.** Targeted cholera surveillance was collaboratively pursued by a multi-institutional consortium comprised of the National Institute of Health Research and Development (NIHRD/LITBANGKES), Directorate General of Communicable Disease Control and Environmental Health and Sanitation (P2M-PLP) and the U.S. Naval Medical Research Unit No. 2 (NAMRU-2), all located in Jakarta. Additionally, local, district, and provincial health offices and selected area hospitals were integrally involved in all aspects of surveillance activities. Cholera surveillance efforts were initiated in 1993 and have continued through 1999. A two-fold approach to comprehensive surveillance focused on investigation of selected diarrheal outbreaks to ensure archipelago-wide coverage of epidemic and sporadic cholera transmission.

**The area.** As an archipelago nation that extends from the Pacific Ocean to the Indian Ocean, Indonesia is made up of 17,000 islands, approximately 5,000 km from east to west. The country’s five principal island chains are characterized by lush, tropical forests, and are crisscrossed by rivers and streams. Most of the cities are congested, with significant overcrowding, particularly in impoverished areas lacking in basic water and waste sanitation. Approximately 34% of Indonesia’s 205 million inhabitants live in urban areas. Significant population migrations resulting from economic, social, and political upheavals have contributed to failures in infrastructure development designed to provide an improved living environment.

**Outbreak investigations.** Seventeen investigations involving suspected diarrheal epidemic occurrence were conducted throughout Indonesia over a seven-year period of targeted cholera surveillance beginning in 1993 and continuing through 1999. Four outbreaks were in Sumatra, five in Java, two in Kalimantan (Borneo), two in Nusa Tenggara, three in Papua (formerly Irian Jaya), and one in Sulawesi (Figure 1). Outbreak selection for investigative purposes was predicated on established criteria that included 1) suspected occurrence involving > 25 persons, 2) associated (reported) fatalities, and 3) timely information allowing for a prompt response during actual epidemic transmission. Additionally, subjective political and security considerations affected outbreak response decisions. Each selected outbreak was investigated...
according to a prescribed protocol, which provided for voluntary and informed consent of study subjects, systematic case sampling (the ratio dependent on the overall number of recognized patients), and age/sex matched healthy controls. Also, a standardized questionnaire was administered in the local dialect by a trained interviewer, providing a demographic and clinical profile of the affected population. Case and control subjects were accessioned from both hospital and community-based (with the household serving as the principal sampling unit) populations. Rectal swab samples were obtained by standard collection procedures and immediately placed in Cary-Blair transport medium for prompt delivery to NAMRU-2 and NIHRD/LITBANGKES, Jakarta.

Cholera surveillance in Indonesia was initiated following protocol driven review by the NAMRU-2 Committee for Protection of Human Subjects (CPHS). Additionally, institutional reviews by the Indonesian Ministry of Health, namely (NIHRD/LITBANGKES) and P2M-PLP were carried out independently, for human use consideration.

Hospital-based monitoring. Selection of hospital sites for the Cholera Surveillance Network (CSN) was intended to provide the widest geographic representation of the archipelago, in the absence of any standardized, laboratory supported monitoring activities, to specifically target sporadic (community-acquired) cholera. Eight public hospitals providing care to the general population were entered into the CSN: one from Java (Jakarta), two from Sumatra (Padang and Medan), one from the Riau Islands (Batam), one from Kalimantan (Pontianak), one from Sulawesi (Makassar), and two from Bali (Denpasar) (Figure 1). Findings represent patient data from 6,882 case subjects enrolled from September 1994 to November/December 1999.

Criteria used in the screening of diarrheal patients for study inclusion purposes reflected severity on actual case admission: debilitating diarrhea with dehydration. After informed, voluntary consent was obtained, demographic patient information pertaining to age and sex was recorded. Two rectal swab samples were obtained from each subject, and placed in Cary-Blair transport medium. Specimens were then transported overnight for isolation and identification at NAMRU-2/LITBANGKES in Jakarta, Indonesia.

Laboratory testing. Rectal swab samples were streaked directly onto a thiosulfate citrate bile sucrose (TCBS) agar, and also placed in alkaline peptone water enrichment broth, and incubated at 37°C. Inoculated enrichment broth was then subcultured to TCBS after 24 hr of incubation. All TCBS plates were incubated at 37°C for 18–20 hr. Yellow colonies resembling those of *V. cholerae* were picked and identified by conventional biochemical and serologic methods. Vibrio cholerae isolates were confirmed on the basis of the following criteria: 1) found to be motile; 2) producing an alkaline slant over an acid butt on Kligler’s iron agar; 3) oxidase, sucrose, indole, ornithine, and lysine positive; and 4) arginine negative. Isolates agglutinating to *V. cholerae* O1 polyvalent antiserum were further characterized by serology with Ogawa- and Inaba-specific antisera. Susceptibility to polymyxin B<sup>16</sup> and the CAMP test<sup>18</sup> were used to differentiate *V. cholerae* O1 from O139 serotype. *Vibrio cholerae* non-O1, O139 serotype<sup>19</sup>. All media used for biochemical testing of *V. parahaemolyticus* contained 1% NaCl. Salt tolerance media were prepared from 1% peptone, 0.1% glucose, 0.006% phenol red, pH 7.4, with (6.5%) and without NaCl. Identification of *V. parahaemolyticus* was performed by a standard culture method. Briefly, isolates that produced an alkaline slant over acid butt on Kligler’s iron agar, and which were motile, and oxidase, indole, lysine, and ornithine positive, but sucrose and arginine negative, were described as *V. parahaemolyticus*. Isolates grew in medium with high salt content (6.5% NaCl), and did not grow in salt-free medium. Arabinose was generally fermented.

Climatic information. Rainfall data (mm) were obtained from the Meteorology and Geophysics Institute, located in Jakarta, Indonesia. Mean cumulative rainfall values from area-specific collection sites were averaged, providing monthly comparative findings from 1993 through 1999.

**RESULTS**

Outbreak findings. The relative importance of *V. cholerae* O1 in epidemic diarrheal transmission is reflected in the laboratory recognition of this bacterial pathogen in every instance of investigated outbreak occurrence. Uniformity in outbreak causation is further demonstrated in that all 17 investigated episodes of epidemic diarrheal disease were attributed to *V. cholerae* O1 of the El Tor biotype, Ogawa serotype. Overall, 27% (95% confidence interval [CI] for proportion = 0.241–0.303) of 788 diarrheal stool samples, representing outbreak specimen collections from throughout the archipelago, cultured positive for the Ogawa serotype. The recovery of Ogawa in stool specimens ranged from 6% of 82 outbreak cases in Jakarta, Java, to 72% of 36 outbreak cases in Aceh, Sumatra (Table 1). Only in one instance involving epidemic diarrheal transmission, in Pontianak, West Kalimantan (1994), was *V. cholerae* O1, Inaba serotype detected, although Ogawa was again implicated relative to outbreak causation: 8% in Inaba versus 18% in Ogawa, among 80 stool samples examined. No *V. cholerae* non-O1 (including the O139 serotype) was identified from cultured isolates.

Overall, the proportional age distribution of outbreak affected case populations pooled from eight investigations was 25%, 13%, 16%, 18%, 8%, 7%, and 3% for the ages < 5, 5–9, 10–18, ranging from 1 to 80 years. However, mean age varied significantly (P < 0.0001) between outbreaks, from a low of 14 years (95% CI for mean = 10–18), ranging from 1 to 80, for the Bandung/Kuningan, Java outbreak of 1997, to a high of 33 years (95% CI for mean = 23–43), ranging from 2 to 80, for the Padang, Sumatra outbreak of 1998 (95% CI for difference between means = 10–29). The overall male-to-female ratio for outbreak cases was 1:1.1.

Anti-microbial susceptibility of *V. cholerae* O1 isolates was 100% for all drug challenges (ampicillin, chloramphenicol, tetracycline, trimethoprim-sulfamethoxazole, ceftriaxone, ciprofloxacin, norfloxacain, and nalidixic acid) except for colistin, for which resistance among 235 isolates was 100%.

Hospital-based findings. Overall, 9% (609 of 6,882 stool
specimens obtained from eight surveillance sites in Sumatra, Bali, Kalimantan, Sulawesi, and Java, representing acute, sporadic cases of debilitating diarrheal disease, were culture positive for *V. cholerae*: 589 (9%) for O1 and 20 (<1%) for non-O1 strains (Table 2). Significant (*P* < 0.0001) proportional variability in *V. cholerae* O1 representation among rectal swab samples was recognized from different hospitals, ranging from 13% (191 of 1,423) in Jakarta, Java to 0% of 272 from Batam, with a mean of 7% (95% CI for the mean = 2.66–11.7). The largest number of *V. parahaemolyticus* isolates (70) came from Bali, but the largest proportion relative to the overall collections came from Makassar (3% of 554). Ogawa serotype was recognized as the principal (98%) one among *V. cholerae* O1 isolates, with a negligible amount of Inaba. This mixture of Ogawa and Inaba serotypes was consistent at all hospital sites except in Medan, where Inaba accounted to 24% of all *V. cholerae* O1 serotype. Additionally, *V. parahaemolyticus* was cultured from 2% (121) of the rectal swabs. Finally, *V. cholerae* non-O1 was cultured from rectal swabs reflecting sporadic cases of diarrheal disease throughout Indonesia: 12 from Bali, two from Padang, three from Jakarta, two from Makassar, and one from Medan. None of the non-O1 isolates proved positive for the *V. cholerae* non-O1, O139 serotype. Notably, no pathogenic vibriomaceae was isolated from 272 rectal swab specimens collected from Batam.

The overall mean age of patients from whom *V. cholerae* O1, *V. cholerae* non-O1, and *V. parahaemolyticus* isolates were cultured was 25 years (95% CI for the mean = 23–24), 35 years (95% CI for the mean = 22–47), and 38 years (95% CI for the mean = 35–41), respectively. Diarrheal cases that proved “other than” cholera by culture method averaged 35 years of age (95% CI for mean = 29.8–39.5). There was significant (*P* < 0.001) geographic variability in mean age by hospital sites for *V. cholerae* O1, ranging from five years (95% CI for mean = 3.43–5.78) in Medan to 29 years (95% CI for mean = 26.9–30.5) in Jakarta. Overall differences in gender case representation, expressed as male-to-female ratios involving diarrheal episodes of biotypes *V. cholerae* O1 (1.1:1), *V. cholerae* non-O1 (1.4:1), *V. parahaemolyticus* (1:1), and non-*Vibrio* bacterial pathogens and viral agents (1:1) showed little variation. For *V. cholerae* O1 in particular, sex ratios differed from 0.8:1 in Jakarta to 1:1.5 in Medan.
There was no in vitro drug resistance associated with the 589 *V. cholerae* O1 isolates tested, except for colistin (100%). A similar antibiotic resistance profile was identified for *V. cholerae* non-O1 and *V. parahaemolyticus* relative to colistin: 83% of 20 isolates and 69% of 121 isolates, respectively. However, anti-microbial susceptibility was observed in 100% of the isolates for chloramphenicol, tetracycline, trimethoprim-sulfamethoxazole, ceftriazone, ciprofloxacin, norfloxacin, and nalidixic acid, whereas 30% of *V. cholerae* non-O1 and 9% of *V. parahaemolyticus* isolates were found to be resistant to ampicillin.

**Climatic and seasonal influences.** Epidemic *V. cholerae*. Relatively low rainfall was recorded during outbreak periods of *V. cholerae* in the western portion of Indonesia, except for Sumatra, where there was no observed correlation between rainfall and the four instances of epidemic occurrence. In Kalimantan, however, the mean cumulative rainfall during the two identified outbreak months was significantly ($P < 0.0001$) less than for the non-outbreak months: 13 mm (ranging from 11 mm to 14 mm) versus 194 mm (ranging from 2 mm to 331 mm). Similarly, the cumulative mean rainfall during the five recognized outbreak periods (35 mm, ranging from 5 mm to 89 mm) in Java was significantly less than for the non-outbreak months (143 mm, ranging from 0 mm to 384 mm). East of this region, beyond the original 1863–1880 geographic/ecologic archipelago divide referred to as Wallace’s Line

\[^{20}\] (Figure 1), outbreaks were more, rather than less, likely to occur during periods of heavy rainfall. The mean cumulative rainfall totals for outbreak versus non-outbreak months varied substantially in Nusa Tenggara and Sulawesi: 317 mm versus 119 mm ($P < 0.05$) and 385 mm versus 177 mm ($P > 0.09$), respectively. Finally, seasonality associated with outbreak occurrence was recognized as somewhat area specific in that two of four outbreaks occurring in Sumatra took place in March (1995 and 1997), five of seven in Kalimantan (1994 and 1997) and Java (1993, 1994, and again in 1994) during September/November, and three of three in Nusa Tenggara (1993 and 1994) and Sulawesi (1998) in March. There was less evidence of seasonal clustering of outbreaks from Papua (Figure 2 A–F).

**Sporadic *V. cholerae*.** In Sumatra (Medan), negligible variability in rainfall over the 64 months of hospital-based surveillance precluded analysis relative to sporadic diarrhea attributed to *V. cholerae*. The only instance (September 1977) in which sporadic *V. cholerae* cases were detected in large numbers, 16 cases from West Kalimantan (Pontianak), occurred when monthly rainfall totaled only 14 mm, compared with a cumulative monthly mean of 196 mm for the other 81 months monitored ($P < 0.0001$). In the relatively short period (42 months) of sporadic disease surveillance from Java (Jakarta), there was evidence that notable spikes of sporadic *V. cholerae* cases may have been a function of low rainfall, whereas in more eastern Nusa Tenggara (Denpasar, Bali) and Sulawesi (Makassar), the relationship between rainfall and increases in sporadic case episodes of *V. cholerae* was less apparent (Figure 2 A–F).

However, two of the four outbreaks investigated from this region did occur during the month of March, both in 1996 and 1998. In Kalimantan, the mean cumulative rainfall during the two identified outbreak months was significantly less than for the non-outbreak months: 13 mm versus 194 mm. Notable is that both outbreaks also occurred during September (1994 and 1997). Similarly, outbreak episodes in Java shared the same climatic and monthly characteristics with Kalimantan in that cumulative rainfall (35 mm) averaged significantly less than for non-outbreak months, and three of the five described outbreaks took place during a September/October (1993 and 1994) temporal window (Figure 2 A–F).

**Temporal relationships between 1.) sporadic and epidemic *V. cholerae* and 2.) non-*V. cholerae* and *V. cholerae*.** A pronounced temporal correspondence was evident between epidemic and sporadic *V. cholerae* from Kalimantan, Java and Nusa Tenggara. Outbreak episodes were generally framed against upward spikes of sporadic case detection. However, there was no observed temporal association between epidemic and sporadic occurrence in Sumatra and Sulawesi (Figure 2 A–F).

Although the small number of sporadic *V. cholerae* cases relative to non-*V. cholerae* diarrheal episodes precluded quantitative comparative analysis of trends, patterns in Sumatra and Java parallel each other. Similarly, although less obvious, was the pattern of occurrence observed in Kalimantan, Nusa Tenggara, and Sulawesi.

**DISCUSSION**

Comprehensive surveillance for epidemic and sporadic diarrheal case detection yielded no *V. cholerae* non-O1 of the O139 serotype. As late as 1995, *V. cholerae* O139 serotype was feared to be an unstoppable juggernaut, displacing the dominant El Tor cholera biotype on its easterly progression across Southeast Asia.

\[^{21}\] Indeed, an early report warned, “Given the rapid spread of *V. cholerae* O139 throughout and beyond the Indian subcontinent, the pandemic potential of these strains seems assured”.\[^{8}\] In Indonesia, this conclusion was drawn against an environmental background already predisposed to epidemic and endemic *V. cholerae* El Tor biotype, namely a poorly developed water sanitary infrastructure.\[^{12}\] However, such supposition has not been borne out in Indonesia, as reflected in our surveillance findings, nor elsewhere in the region.\[^{23}\]

Outbreak investigation as an integral component of surveillance strategy provided a unique opportunity to identify the cause of epidemic diarrheal disease. Most notable was the ubiquitous predominance of cholera, specifically the Ogawa serotype, in epidemics throughout the archipelago. Comparative outbreak data from other countries/regions are sparse, since epidemic occurrence has not been investigated in a systematic manner as part of a coordinated surveillance activity, particularly in developing areas. Surveillance findings presented in this report arm Indonesian health authorities with important etiologic information for mounting appropriate preventive and therapeutic actions, principally in presumptive cholera outbreaks, in the absence of prompt confirmatory laboratory results. The findings also facilitate appropriate clinical case treatment and management strategies, as well as outbreak containment measures. Additionally, pre-emptive cholera vaccine (constructed for the Ogawa serotype) intervention in the early phases of outbreaks of explosive diarrhea may be warranted.

As with epidemic surveillance efforts, managed (hospital-
based) networks targeting sporadic cholera disease are still a rarity in much of the developing world. Even along the gulf coast of the United States, an area historically plagued by cholera, coordinated multi-state *Vibrio* surveillance was only initiated in 1989. In Indonesia, surveillance findings show the proportional representation of *V. cholerae* among sporadic diarrheal episodes to be variable by location, although the El Tor, Ogawa serotype was ubiquitous. The El Tor biotype is spread by shedding of the organism into the environment from healthy persons, more so than the classical...
biotype. This characteristic assures the predominance of El Tor relative to classical biotype, regardless of whether in epidemic or sporadic form.\textsuperscript{22,24}

The relatively high proportion of sporadic cholera cases recognized in Jakarta (13\%) may reflect the notoriously polluted coastline along which much of the city’s human refuse is deposited. This provides a suitable warm, stagnant environment of high salinity favoring microbial growth and fecal-oral spread via consumption of contaminated shellfish, fruits, and water.\textsuperscript{21} In another study, the rate of cholera in Jakarta (1993–1997), identified from a “passive system” of hospital-based surveillance for cholera vaccine evaluation purposes, was 7,442 cholera cases/100,000 diarrheal episodes, or 7\%, of which all were the El Tor Ogawa serotype.\textsuperscript{12} In yet another study, targeting pediatric hospitalized diarrheal episodes in Jakarta in 1988–1989, less than 3\% of cases
SULAWESI

F

PAPUA

\[\text{Diarrheal outbreak occurrence}\]

FIGURE 2. continued.
were attributed to *V. cholerae*. However, the comparability of these data may be limited because the proportional representation of cholera cases is likely a function of hospital study geographic locations and associated catchment areas within Jakarta. Hospitals from northern Jakarta, where the highest rates of cholera were observed, tend to serve a more indigent population living in relatively poor environmental sanitary conditions.

The importance of sporadic cholera occurrence in Bali (10%), second only to Jakarta, has also been highlighted by documented cases of acquired cholera in Singaporean and Japanese travelers to Bali in 1991. In contrast to findings from other surveys conducted in 1961–1980, 1965–1991, and 1975–1981 on travelers returning to Europe and North America, cholera rates were generally less than 1/100,000. Such vacations reflected few Bali travel destinations. The rate among Japanese tourists returning from Bali was 13.1/100,000. However, these observations may be confounded by a Japanese taste preference for local, raw seafood products. Nonetheless, this rate of imported cholera was significantly higher than from for any other world-wide tourist or business destination, regardless of the home region surveyed. Negligible drug resistance was identified among isolates obtained from both epidemic and sporadic clinical settings. The exception to this was resistance to colistin, again, in instances of both epidemic and sporadic cholera. Antimicrobial resistance is becoming problematic in many areas of the developing world, including Southeast Asia, because antimicrobial drugs are inexpensive and relatively unrestricted in availability. In India, most cholera strains were shown to be resistance to co-trimoxazole, (trimethoprim-sulfamethoxazole): 96% and 86% from Tamil Nadu and Calcutta, respectively, whereas 100% of isolates were susceptible to tetracycline. Laboratory data from Bangladesh show high resistance (> 50%) in *V. cholerae* isolates to tetracycline and trimethoprim-sulfamethoxazole, whereas negligible resistance was identified for doxycycline and diprofloxacin. High antimicrobial sensitivity from Indonesia did not allow for analysis of trend over time.

Cholera occurrence has been shown to be a function of predisposing climatic influences such as water temperature. Changes in local sea surface temperatures brought on by such weather anomalies as the El Niño-Southern Oscillation have been suggested to be related to the spread of tens of thousands of new cases of cholera. Increases in surface temperature brought on by El Niño resulted in warmer winter temperatures, which correlated with a doubling of pediatric cases in Peru. Less clear has been the relationship between rainfall and exposure opportunities associated with cholera risk. Certainly, heavy rains leading to excessive flooding have the potential of contaminating water supplies, as described in numerous instances around the world. Conversely, subnormal rainfall may result in decreased dilution and increased concentration of *V. cholerae* bacteria, translating into increased risk of exposure. A similar phenomenon has been documented favoring epidemic transmission of leptospirosis and hepatitis E virus.

In Indonesia, differences in temperatures, particularly along coastal sections are slight, precluding causal analysis. Surveillance data coupled with rainfall measures afford a unique opportunity to identify correlations between rainfall and cholera. In western Indonesia, in contrast with the eastern part, epidemic and sporadic *V. cholerae* appear correlated with periods of subnormal rainfall. A similar phenomenon was discerned from surveillance findings reported from Jakarta, where hospitalized cases peaked following and just prior to the “first” and “second” rainy seasons. Likewise, data extrapolated from hospital based surveillance in Jakarta (1993–1997) showed increases in detection of cholera cases coinciding with drier rather than wetter weather (Simanjuntak C. and Punjabi N, unpublished data). However, this temporal relationship shifts in the more eastern portion of the archipelago, where outbreak occurrence in fact appears during periods of heavy rainfall. Additionally, seasonal trends in epidemic cholera vary with geography: September and October in the west, and February through April in the east.

The need for surveilance data, including targeted outbreak findings, is essential in plotting the introduction and spread of endemic and pandemic cholera. Vigorous attention to systematic, on-going collection efforts, particularly in more developing areas traditionally associated with cholera occurrence, requires a well coordinated and managed surveillance approach. This report describes the first such system implemented in Indonesia for recognizing the introduction of the new *V. cholerae* non-O1, O139 serotype. Surveillance findings provided a unique geographic profile of cholera, both in the epidemic and sporadic forms. Most notable was the demonstration of cholera as the principal cause of epidemic diarrheal disease throughout the archipelago, the implications of which are being factored into future intervention and control strategies.

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